REMARKS

Entry of the response and reconsideration of the application are respectfully requested. After entry of the response, claims 1-32, 40, 41 and 44-92 will be pending. Claims 14, 52 and 74 have been amended to remove reference to humanized C242 so that such reference can be made in new claims 90, 91 and 92. No new matter is added by these amendments. Claims 1-32 have been previously withdrawn by the Examiner from further consideration pursuant to 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention and the Examiner has made the restriction requirement final. The Examiner stated in the previous Action mailed May 24, 2002 that claims 1-32 will be subject to rejoinder at applicant's request once claims 40, 41 and 44-89 are directed to an allowable product. The Examiner further mentions that process claims, which do not depend from or otherwise include all the limitations of an allowable product, will not be rejoined.

Various claims stand rejected under 35 U.S.C. § 112, first and second paragraph, and under 35 U.S.C. § 103(a). Each rejection will be addressed below. In light of the discussion below, it is believed that that above rejections of record have been overcome and that all pending claims are in condition for allowance. Action towards this end is respectfully requested.

I. Rejections under 35 U.S.C. § 112, first paragraph

The specification is objected to and claims 52 and 74 stand rejected under 35 U.S.C. § 112, first paragraph, as it is asserted that the specification fails to provide an adequate written description of the invention and fails to provide an enabling disclosure because the specification fails to provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description; or (3) deposited. In response to applicant's assertions that that the monoclonal antibodies C242 and N901 are known in the art and can be produced without undue experimentation, the Action states that the Manual of Patent Examining Procedure § 2401.01 "states to avoid the need for a deposit, biological materials must be known and readily available – *neither concept alone suffices.*" (Emphasis in original). The rejection is hereby traversed for the following reasons.

A biological deposit "is not necessary even though specific biological materials are required to practice the invention if those biological materials can be made or isolated without undue experimentation." *Manual of Patent Examining Procedure § 2404.02* (2001). The rejection is therefore traversed, as such antibodies may be produced by the skilled artisan without undue experimentation by producing, for example, murine monoclonal antibodies and humanizing the antibodies, both by published methods well known to the skilled artisan and cited in the application.

Monoclonal antibody technology is a mature technology; it has existed at least about 28 years, and antibody humanization methods have existed at least about 10 years. As mentioned on page 16, line 26 to page 17, line 1, of the application: "Particularly well known in the art are techniques for creating monoclonal antibodies produced by immunizing mice, rats, hamsters or any other mammal with the antigen of interest such as the intact target cell, antigens isolated from the target cell, whole virus, attenuated whole virus, and viral proteins such as viral coat proteins." For example, methods of producing C242 are known to the art and described in U.S. Patent No. 5,552,293 (submitted as Exhibit A in Response mailed May 24, 2002, Paper No. 17) as mentioned on page 18, lines 19-22, of the application.

Example 1, column 5, lines 45-66, of U.S. Patent No. 5,552,293 (the '293 patent) describes immunizing BALB/c mice with a commercially available human colorectal carcinoma cell line and isolating the spleens of the mice. Column 5, line 66, to column 6, line 27, of the '293 patent describes preparation of a hybridoma by fusing the spleen cells obtained from the spleens with commercially available mouse myeloma cell line Sp2/0. Screening of the antibody-secreting hybridomas and subsequent cloning of the hybridomas is described in column 6, line 28 to column 7, line 38, of the '293 patent. Production of the C242 antibody is described in column 7, lines 39-60, and purification of the antibody is described in column 7, line 62 to column 8, line 12, of the '293 patent. Indeed, even the nucleotide and its corresponding amino acid sequences of the variable domain of the kappa and heavy chain of the C242:II monoclonal antibody is provided in the '293 patent.

Methods of producing N901 are also known to the art, as evidenced by Griffin et al., *J. Immunol.*, 130(8):2947-2951 (1983) (submitted as Exhibit B in Response mailed May 24, 2002, Paper No. 17; and recited on page 17, line 30 of the application). For example, immunization of

BALB/c mice with leukemic cells, somatic cell hybridization by the method of Kohler and Milstein with described modifications, screening by indirect immunofluorescence and cloning is described on page 2947, column 2, lines 16-26, of Griffin *et al.*

Notwithstanding this ability of the skilled artisan to produce such antibodies, a hybridoma cell line having use in the invention and producing a C242 antibody was deposited by an entity unrelated to the present inventor at the European Collection of Animal Cell Cultures (ECACC) in the United Kingdom under depository accession number 90012601. Included herein as Exhibit F is a Certification from the U.S. Patent and Trademark Office under 37 CFR 1.808(c), certifying the deposit of this hybridoma under the Budapest Treaty.

Once murine hybridomas are obtained for the respective antibodies, the antibodies may be humanized **without undue experimentation** by application of different humanization technologies known to the art and described, for example, in U.S. Patent Nos. 5,225,539 (submitted as Exhibit C in Response mailed May 24, 2002, Paper No. 17); 5,585,089 (submitted as Exhibit D in Response mailed May 24, 2002, Paper No. 17); and 5,639,641 (submitted as Exhibit E in Response mailed May 24, 2002, Paper No. 17); as mentioned in the application on page 18, lines 25-28. Additionally, methods of producing different versions of humanized N901 have been specifically described in the scientific literature. See, for example, Roguska *et al. Proc. Natl. Acad. Sci. USA*, 91:969-973 (1994) and Roguska *et al. Protein Eng.*, 9:895-904 (1996) mentioned on page 18, lines 28-30, of the application. Both of these Roguska *et al.* references were previously submitted in an Information Disclosure Statement for the present application.

For example, humanized N901 has been produced by a "resurfacing" process described in Roguska *et al., Proc. Natl. Acad. Sci*, 91:969-973 (1994). Briefly, in such a process, the complementarity-determining regions (CDRs) and the core of the murine variable region framework were maintained and the surface residues of the framework region were replaced with those from a human variable region. After obtaining, for example, the cDNA of N901 from a murine hybridoma and resurfacing N901 V_H and V_L genes as described on page 970, column 1, of Roguska *et al.* (1994), the cDNA encoding the resurfaced antibody was transiently transfected into COS cells and the humanized antibody was purified by staphylococcal protein A affinity chromatography as described in Roguska *et al.* (1994). Such a procedure may similarly be

performed for C242 by the skilled artisan without undue experimentation. Therefore, the specification provides a written description that is more than sufficient to enable one skilled in the art to produce humanized versions of C242 and N901 without undue experimentation, and to thereby practice the invention defined by, for example, the rejected claims. There is no basis in the Action for the assertion that such antibodies require undue experimentation for their production.

Additionally, with reference to the concept of known and readily available with respect to biological material, relevant factors that may be used as indicia that a biological material is known and readily available to the public include references to the biological material in printed publications and evidence of predictable isolation techniques. *Manual of Patent Examining Procedure* § 2404.01 (2001). The biological material in question is mentioned in the printed publications on pages 11 and 12 above. For example, humanized N901 is discussed in, for example, Roguska et al. (1994 and 1996). Moreover, as further evidenced by the publications discussed above on pages 11 and 12, predictable and well-known isolation techniques are available to produce humanized N901 and humanized C242. Withdrawal of the rejection of claims 52 and 74 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 52 and 74 stand rejected as it is asserted that claims 52 and 74 are indefinite due to the use of the designations "N901" and "C242" as the sole means of identifying the humanized antibodies to which the claims refer. It is further asserted that the use of laboratory designations only to identify a particular antibody renders the claims indefinite because different laboratories may use the laboratory designations to define completely distinct antibodies. It is additionally asserted that "[t]o distinctly claim and particularly point out a specific biological material requires the use of a unique identifier, e.g., the recitation of the name of a particular depository and the number under which the deposit has been made; the recitation of the particular amino acid sequence of a polypeptide; the recitation of the particular polynucleotide sequence of a nucleic acid molecule."

As the Office is aware, "the definiteness of the language employed [in a claim] must be analyzed - not in a vacuum, but always in light of the teachings of the prior art and of the

particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 169 U.S.P.Q. 236, 238 (C.C.P.A. 1971). Not only has the Action not provided evidence that other laboratories use the designations in question for completely different antibodies, one skilled in the art, especially in light of the specification which specifically references publications particularly describing N901 or C242 antibodies (see, *e.g.*, page 17, line 27 to page 18, line 2; and page 18, lines 19-22, of the specification), is well-aware of the metes and bounds of the claims referring to N901 and C242.

Moreover, with respect to the designation "C242", other publications from different laboratories refer to the C242 antibody. For example, Haglund *et al.*, *Br. J. Cancer* 60(6):845-851 (1989) (included herein as Exhibit G) ; Larson *et al.*, *Int. J. Cancer* 42:877-882 (1988) (included herein as Exhibit H); and Rothnie *et al.*, *Gut* 31:AG19 (1990) (included herein as Exhibit I) all refer to antibody C242 as a monoclonal antibody raised after immunization of mice with Colo 205, a human colonic adenocarcinoma cell line. Rothnie *et al.* and Haglund *et al.* further mention that monoclonal antibody C242 binds to antigen CA 242 having a sialated carbohydrate structure. Dohlstein *et al.*, *Proc. Natl. Acad. Sci USA* 88:9287-9292 (1991) (included herein as Exhibit J) refers to C242 as reacting with human colon cancer. Therefore, the designation "C242" would be considered definite to the skilled artisan.

Moreover, with respect to the designation "N901", this designation is recognized in the scientific community as a reference to an antibody that binds to a specific leucocyte differentiation antigen. For example, Exhibit K, pages 699-702 and 1088, from a publication entitled "Leucocyte Typing IV, White Cell Differentiation Antigens", Knapp, *et al.*, Eds., Oxford University Press, 1989, discusses the conclusions of a workshop periodically convened to group such antibodies according to the leucocyte antigen to which they bind. Such groups are called Clusters of Differentiation (CD). Exhibit K demonstrates that N901 was found to belong to CD56, and is therefore recognized as an antibody that binds to the CD56 antigen.

Additionally, the scientific industry refers to N901 as an antibody that binds to the CD56 antigen. This can be seen in the sales literature of Beckman Coulter, which sells N901 commercially, included herewith as Exhibit L. Therefore, the designation "N901" would be considered definite to the skilled artisan. Withdrawal of the rejection of claims 52 and 74 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

III. Rejection under 35 U.S.C. § 103(a)

Claims 40, 41 and 44-89 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Liu *et al.* [*Proc. Natl. Acad. Sci. USA* 93:8618-8623 (1996)] in view of Mendelsohn [*Clinical Cancer Res.* 3:2703-2707 (1997)] and Hortobagyl [*Oncology* 11:11-15 (1997)] for the reasons set forth in the previous Office Action mailed May 24, 2002.

A. Rejections stated in Office Action mailed May 24, 2002

Liu *et al.* was relied on for teaching an immunotoxin comprising a humanized antibody (C242) that is conjugated to a maytansinoid and also for teaching "a chemotherapeutic agent, namely 5-fluorouracil (5-FU)". It is admitted in the Action that Liu *et al.* do not teach a kit and do not teach a composition of an immunoconjugate and a chemotherapeutic agent.

Mendelsohn was relied on for teaching that combining a therapeutic chimeric antibody with a chemotherapeutic drug successfully eradicates well-established tumor xenografts that resist treatment with either agent alone.

Hortobagyl was relied on for teaching (1) a rationale for combination therapy; (2) many different chemotherapeutic agents, including paclitaxel, vinorelbine, etoposide, cisplatin and doxorubicin and that combinations of docetaxel and other agents have been shown to be highly active in preclinical mode; and (3) that synergies, or at least additive effects, were observed in studies with two- and three-drug combinations.

It was concluded in the Action that it would have been prima facie obvious to one of ordinary skill in the art to manufacture a kit comprising at least one, if not several, chemotherapeutic agents currently in development and widely known in the art. It was asserted one skilled in the art would have been motivated to manufacture such a kit because "the kit could be used to find effective combinations, strategies and regimens, and to determine optimal roles for one agents [sic] in relation to the others". It was further concluded in the Action that it would have been prima facie obvious to make a composition comprising one or the other immunoconjugates of Liu *et al.* and further comprising at least one of the chemotherapeutic agents currently under development and widely known in the art. It was asserted that one of ordinary skill in the art would have been motivated to determine if a combination of the immunoconjugate of Liu *et al.*, and one or more of the chemotherapeutic agents "be [sic] more effective than any of the agents alone, since both Mendelsohn and Hortobagyl teach that

combination therapy is often more effective than monotherapy because synergistic or additive effects are often observed in the former."

B. Applicant's position

1. Applicant's assertions discussed in the Response (mailed August 23, 2002) to the Office Action mailed May 24, 2002

Applicant asserted in the response mailed August 23, 2002, *inter alia*, that Liu *et al.* teach away from the claimed invention and that unexpected results were obtained. In response, the Action states (1) "as kits were so highly prevalent in the art at the time the application was filed, the motivation to manufacture a kit comprising one chemotherapeutic agent and at least one immunoconjugate comprising a humanized antibody, namely C242 or N901, and an anti-mitotic agent would have been found in the knowledge generally available to one of ordinary skill in the art; (2) given the teachings of Liu *et al.*, Mendelsohn and Hortobagyl, one skilled in the art would have been motivated to manufacture the kit because "such a kit could be used to find effective combinations, strategies, and regimens, and to determine the optimal roles for one of the agents in relation to the others;" and (3) that applicant's contention that "additive or synergistic effects of combinations of anticancer agents would have been unexpected by one of ordinary skill in the art is baseless" and "nonetheless, both Mendelsohn and Hortobagyl teach combinations of anticancer agents and suggest a rational for producing the combinations: the frequent observation of additive or synergistic effects." The Action also states that other prior art made of record in the previous Office Action provides evidence that one skilled in the art would not have found any observed additive or synergistic effect of a combination of anticancer agents either surprising or unexpected. In reference to the aforementioned prior art made of record in the previous Office Action, applicant notes that only the specific rejections based on specified prior art are addressed in this response. Applicant will address any other rejections based on any combination of the 27 references cited in the previous Office Action if such rejections and references are stated with particularity.

2. Applicant's response to Action's assertions

Applicant asserts there is no teaching, suggestion or motivation to combine Liu *et al.* with Hortobagyl and Mendelsohn, as suggested in the Action, because Liu *et al.* teach away from such a combination and, even if such a combination was made, the observed efficacy of the claimed kits and compositions would not have been expected.

As the Office is aware, a conclusion of "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so." *ACS Hospital Sys. Inc., v. Montefiore Hospital et al.*, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984) (Emphasis in original). "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *Manual of Patent Examining Procedure* § 2141.02; *See W.L. Gore & Associates, Inc. v. Garlock, Inc.* 220 U.S.P.Q. 303, 311 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 851 (1984).

Liu *et al.* must be considered in its entirety, i.e., for its teaching **as a whole**. Liu *et al.* teach that the immunoconjugate C242-DM1 was "**highly cytotoxic** toward cultured colon cancer cells in an antigen-specific manner and showed remarkable anti-tumor efficacy in vivo." (Emphasis supplied.) It was further found that injections of C242-DM1 in animals bearing COLO 205 tumors resulted in complete tumor regression lasting 5 weeks and no indication of toxic side effects as assessed by body weight loss was observed as recited on page 8622, column 1, of Liu *et al.* It is further mentioned in the same column that tumors treated with 5-FU grew rapidly to large sizes. Additionally, it is further mentioned in the Discussion section of the paper on page 8622, second column, that "5-FU, the standard chemotherapeutic drug used for the treatment of colorectal cancer, showed very little therapeutic benefit against the same tumors." After reviewing Liu *et al.*, at most, one skilled in the art would be motivated to utilize the immunoconjugate C242-DM1 alone, because Liu et al., **as a whole**, teaches the immunoconjugate "showed remarkable anti-tumor efficacy in vivo," allowed for complete tumor regression and had no indication of toxic side effects. Therefore, one skilled in the art would not be motivated to combine Liu *et al.* with Hortobagyl or Mendehlson as Liu *et al.* teaches the effectiveness of monotherapy with no toxic side effects. Why would one skilled in the art

attempt combination therapy with the problems one may encounter, including toxic side effects, when monotherapy allowed for complete tumor regression with no toxic side effects? In fact, due to the Liu *et al.* teaching of the effectiveness of monotherapy leading to complete tumor regression and no indication of toxic side effects, Liu *et al.* also teach away from combination therapy.

Mendelsohn discusses anticancer therapy utilizing doxorubicin or cisplatin in combination with a monoclonal antibody. Hortobagyl discusses treatment of breast cancer and a rationale for combination therapy. The only clinical data discussed in Hortobagyl relating to combination therapy is from a cited reference where docetaxel was assertedly used in combination with two- and three-drug combinations with doxorubicin, cyclophosphamide, fluorouracil, vinorelbine, methotrexate and etoposide. There is no teaching or suggestion in either Mendelsohn or Hortobagyl of a kit or composition that includes at least one immunoconjugate and at least one chemotherapeutic agent as recited in the rejected claims, nor is there any teaching, suggestion, or motivation to combine these references with Liu *et al.* as discussed in the preceding paragraph, to provide a kit or composition that includes at least one immunoconjugate and at least one chemotherapeutic agent as recited in the rejected claims. The assertion in the Action that one skilled in the art would have been motivated to manufacture a kit that includes one chemotherapeutic agent and at least one immunoconjugate comprising a humanized antibody, namely C242 or N901 because "the kit could be used to find effective combinations, strategies, and regimens, and to determine the optimal roles for one of the agents in relation to the others" is no more than an obvious to try rationale. As the Office is aware, **such an obvious-to-try rationale is improper**. *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987) (stating that, "[a]t best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known...agents. However, this is not the standard of 35 U.S.C. § 103"). Any such teaching or suggestion can only come from impermissible hindsight analysis using the applicant's disclosure as a guide. Moreover, there is no teaching or suggestion in Liu *et al.*, Mendelsohn or Hortobagyl, either alone or combined, of the unexpected efficacy of the claimed kits and compositions.

As the Office is aware, secondary considerations must be taken into account in making a determination of obviousness. *See Stratoflex, Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871 (Fed.

Cir. 1983). For example, unexpected results are evidence of non-obviousness. *See In re Corkill*, 226 U.S.P.Q. 1005, 1009 (Fed. Cir. 1985) ("A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue"). Applicant will review their unexpected results and then respond to the Action's current assertions. It should be noted here that applicant asserts observation of unexpected, synergistic effects, not additive effects as asserted in the Action.

In the present case, it has unexpectedly been discovered that claimed compositions of immunoconjugates and chemotherapeutic agents delay tumor growth longer than one would expect for an additive anti-tumor effect of the individual components. For example, in Example 3 of the application, it has unexpectedly been discovered that a tumor growth delay of twelve days was observed when SCID mice with tumors derived from NCI N417 cells were treated with huN901-DM1 in combination with cisplatin and etoposide, whereas a tumor growth delay of four days was obtained in animals treated with either huN901-DM1 or cisplatin and etoposide. The tumor growth delay of 12 days represents a synergistic effect, as it is 50% longer than the eight days one would expect for an additive anti-tumor effect of the individual treatments.

As a further example, as seen in Example 4 of the application, in a similar experiment involving treatment with docetaxel alone, huN901-DM1 alone or a combination of docetaxel and huN901-DM1, treatment with docetaxel or huN901-DM1 alone resulted in tumor growth delays of 8 days and 20 days, respectively. In contrast, treatment with the combination of docetaxel and huN901-DM1 resulted in complete tumor regression in all the treated animals. The tumor was eradicated in 3 out of 6 animals in this treatment group, resulting in cures lasting greater than 200 days. In the remaining 3 animals in this group, there was a tumor growth delay of 52 days, which is 24 days longer than the calculated additive effect of the treatment with docetaxel and huN901-DM1 alone. Other such unexpected, synergistic and otherwise surprising results are found in Examples 2, 5, 6 and 7 of the pending application. Such superior, unexpected, synergistic and otherwise surprising results utilizing the claimed kits and compositions are not taught or suggested in Liu *et al.*, Mendelsohn, or Hortobagyl, either alone or combined.

In response to the Action's assertions that applicant's comments with respect to unexpected results are baseless and that Mendelsohn and Hortobagyl "teach combinations of anticancer agents and suggest a rationale for producing combinations: the frequent observation

of additive or synergistic effects", please consider the following. Notwithstanding the comments in the abstract of Mendelsohn, the results described therein do not teach or suggest that combining a monoclonal antibody, let alone an immunoconjugate as recited in the pending claims, and a chemotherapeutic agent results in expected, synergistic effects. For example, in the section entitled "Hypothesis 5" discussed on page 2705, experiments involving combined therapy with anti-EGF receptor monoclonal antibody with doxorubicin; mAB225 or 528 in combination with cisplatin; and mAB 225 in combination with paclitaxel are described. After describing the results, it is mentioned in the last paragraph of column 1 that "[t]he mechanism of these *additive* effects are under investigation in our laboratory." (Emphasis added).

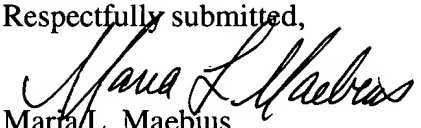
Turning now to Hortobagyl, there is no mention that additive or synergistic effects are "frequent". Hortobagyl states, on page 12, lines 24-30, citing reference 7, that "[s]ynergies, or at least additive effects, were observed in studies with two- and even three-drug combinations, including docetaxel, cyclophosphamide (Cytoxan, Neosar), fluorouracil (5-FU), vinorelbine, methotrexate, and etoposide (VePesid)." Reference 7 is an abstract (abstract number 1946) from Bissery, M.C. et al., *Proc. Am. Assoc. Cancer Res.* 35:327, 1994 and is submitted herewith as Exhibit M. The abstract mentions that docetaxel was evaluated in combination with doxorubicin, 5-fluorouracil, cyclophosphamide, mitomycin C, vincristine, vinblastine and vinorelbine (methotrexate and etoposide were not used as asserted in Hortobagyl). The only results discussed are the maximum tolerated dose of each drug that could be administered in combination without additional toxicity. There is no teaching or suggestion in the abstract that combinations of the specific anticancer agents tested led to synergistic effects.

Additionally, even if these references somehow teach or suggest synergistic effects when combining certain anticancer agents, there is no teaching or suggestion that a composition or kit including at least one chemotherapeutic agent and at least one immunoconjugate as recited in the pending claims would be expected to act in a synergistic fashion as found by applicant. Withdrawal of the rejection of claims 40, 41 and 44-89 under 35 U.S.C. § 103(a) is respectfully requested.

IV. Conclusion

In light of the foregoing, it is believed that all objections and rejections of records have been obviated and that the claims are in condition for allowance. Action towards this end is respectfully requested. The Examiner is invited to telephone the undersigned attorney to discuss any matters that may be handled in that fashion.

Respectfully submitted,



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